Microvascular Invasion Does Not Predict Long-Term Survival in Hepatocellular Carcinoma up to 2 cm: Reappraisal of the Staging System for Solitary Tumors

Published in final edited form as:
Ann Surg Oncol. 2013 April ; 20(4): . doi:10.1245/s10434-012-2739-y.

Microvascular Invasion Does Not Predict Long-Term Survival in Hepatocellular Carcinoma up to 2 cm: Reappraisal of the Staging System for Solitary Tumors

Junichi Shindoh, MD, PhD[1], **Andreas Andreou, MD**[1], **Thomas A. Aloia, MD**[1], **Giuseppe Zimmitti, MD**[1], **Gregory Y. Lauwers, MD**[2], **Alexis Laurent, MD**[3], **David M. Nagorney, MD**[4], **Jacques Belghiti, MD**[5], **Daniel Cherqui, MD**[3], **Ronnie Tung-Ping Poon, MS, FRCS**[6], **Norihiro Kokudo, MD, PhD**[7], and **Jean-Nicolas Vauthey, MD**[1]

[1]International Cooperative Study Group on Hepatocellular Carcinoma, Department of Surgical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX

[2]Department of Pathology, Massachusetts General Hospital, Boston, MA

[3]Department of Digestive and Hepatobiliary Surgery and Liver Transplantation, Hôpital Henri Mondor, Créteil, France

[4]Department of Gastroenterologic and General Surgery, Mayo Clinic, Rochester, MI

[5]Department of Hepatopancreato-biliary and Transplantation Surgery, Beaujon Hospital, Assistance Publique Hôpitaux de Paris, Clichy, France

[6]Department of Surgery, Queen Mary Hospital, The University of Hong Kong, Hong Kong, China

[7]Hepato-biliary-pancreatic Surgery Division, Department of Surgery, University of Tokyo, Tokyo, Japan

Abstract

Background—Excellent long-term outcomes have been reported recently for patients with small (≤2 cm) hepatocellular carcinoma (HCC). However, the significance of microvascular invasion (MVI) in small HCC remains unclear. The purpose of this study was to determine the impact of MVI in small HCC up to 2 cm.

Methods—In 1,109 patients with solitary HCC from six major international hepatobiliary centers, the impact of MVI on long-term survival in patients with small HCC (≤2 cm) and patients with tumors larger than 2 cm was analyzed.

Results—In patients with small HCC, long-term survival was not affected by MVI ($p = 0.8$), whereas in patients with larger HCC, significantly worse survival was observed in patients with MVI ($p < 0.0001$). In multivariate analysis, MVI (hazard ratio [HR] 1.59; 95 % confidence interval (CI) 1.27–1.99; $p < 0.001$), elevated alpha-fetoprotein (HR 1.41; 95 % CI 1.11–1.8; $p = 0.005$), and higher histologic grade (HR 1.29; 95 % CI 1.01–1.64; $p = 0.04$) were significant predictors of worse survival in patients with HCC larger than 2 cm but were not correlated with long-term survival in small HCC. When the cohort was divided into three groups—HCC ≤2, >2 cm without MVI, and HCC >2 cm with MVI—significant between-group survival difference was observed ($p < 0.0001$).

J.-N. Vauthey, MD, jvauthey@mdanderson.org.

DISCLOSURES Authors have no conflict of interest to disclose.

Conclusions—Small HCC is associated with an excellent prognosis that is not affected by the presence of MVI. The discriminatory power of the 7th edition of the AJCC classification for solitary HCC could be further improved by subdividing tumors according to size (≤2 vs. >2 cm).

Multiple staging systems have been proposed for stratifying patients with hepatocellular carcinoma (HCC) according to prognosis and optimal treatment. The 7th edition of the American Joint Committee on Cancer (AJCC) staging system for HCC is one of the most commonly used staging systems, and its usefulness and clinical relevance have been validated by various external studies.[1–8] However, a limitation of the current AJCC staging system is that solitary HCC is not stratified with respect to size. Because the selection of treatment is highly dependent on tumor size in the era of multimodality treatment for HCC, it is practically important to clarify the clinical significance of tumor size using a large international population.

Recently, excellent long-term outcomes in patients with solitary HCC up to 2 cm have been reported in several studies.[9–14] This size cutoff of 2 cm has been adopted in the 5th edition of the Liver Cancer Study Group of Japan (LCSGJ) classification and in the Barcelona Clinic Liver Cancer (BCLC) staging system.[15,16] In addition to tumor size, the presence of microvascular invasion (MVI) has been reported to be a strong prognostic factor in HCC.[17–20] However, the significance of MVI in small HCC has not yet been clarified. Accordingly, the definition of the earliest stage of solitary HCC varies among the staging systems.

Given these areas of ambiguity and the frequent clinical presentation of solitary HCC, the purpose of this study was to clarify the clinical significance of MVI in HCC up to 2 cm to further optimize the current AJCC classification for solitary HCC.

PATIENTS AND METHODS

Study Cohort and Clinicopathologic Variables

The Institutional Review Board of The University of Texas MD Anderson Cancer Center approved this study protocol. We identified 1,975 patients who underwent curative resection of HCC between 1981 and 2011 at six major hepatobiliary centers: MD Anderson Cancer Center (Houston, TX, USA), University of Tokyo (Tokyo, Japan), Mayo Clinic (Rochester, MI, USA), Hôpital Beaujon (Paris, France), Hôpital Henri Mondor (Créteil, France), and Queen Mary Hospital (Hong Kong, China). To permit assessment of prognostic factors in solitary HCC, we excluded patients with multiple tumors (n = 651), major vascular invasion (n = 160), extrahepatic disease (i.e., positive lymph nodes or metastases; n = 17), or tumor invasion of other organs or tumor rupture (n = 34). Four patients with incomplete pathologic data also were excluded from this study. The remaining 1,109 patients comprised the final cohort and were studied in detail.

Patients were considered positive for hepatitis B virus if they had hepatitis B surface antigen or antihepatitis B core antibody. Patients were considered positive for hepatitis C virus if they had antihepatitis C virus antigen. Tumor size was based on the largest dimension of the tumor in the resected specimen. Patients were considered to have MVI if they had microscopic tumor emboli within the central hepatic vein, the portal vein, or the large capsular vessels. Tumor grade was assessed using the scheme outlined by Edmondson and Steiner[21] and was recorded based on the highest grade in a specimen. The degree of fibrosis was assessed on the basis of the Ishak score, and grades F5 and F6 were considered cirrhosis.[22]

Statistical Analysis

Statistical analysis was performed using IBM SPSS software (version 19.0, SPSS Inc., Chicago, IL) and JMP 9.0 software (SAS Institute Japan, Tokyo, Japan). Medians and ranges of continuous variables were compared using the Mann–Whitney *U* test. Categorical variables were compared using Pearson's χ^2 test or Fisher's exact test as appropriate.

The rationale for adopting the cutoff value of 2 cm for solitary HCC was confirmed by the minimum *p* value approach to predict survival after surgical resection. The hazard ratio (HR) was highest and *p* value was lowest at 2 cm (HR 1.83; 95 % confidence interval (CI) 1.37–2.49; $p < 0.0001$) when sliding the cutoff value from 1 cm through 10 cm.

Survival curves were generated using the Kaplan–Meier method and were compared by log-rank test. To determine the interaction between the size cutoff of 2 cm and the presence of MVI, survival curves were compared between the patients with and without MVI stratified by tumor size. To identify prognostic factors, a multivariate regression analysis was performed using the Cox proportional hazard model for the variables with $p < 0.05$ in univariate analysis.

RESULTS

Clinicopathologic Characteristics

The median age of the 1,109 patients with solitary HCC was 62 years (range 4–87); 809 patients (72.9 %) were men. Of the 1,109 patients, 1,030 (92.9 %) were classified as Child–Pugh A, and the remaining 79 patients (7.1 %) were Child–Pugh B. Among the 747 patients for whom the results of hepatitis C virus serologic tests were available, 324 (43.4 %) patients were positive for hepatitis C. Among the 996 patients for whom the results of hepatitis B virus serologic tests were available, 401 (40.3 %) patients were positive for hepatitis B. Median tumor size was 4.8 cm (range 0.5–27), and 155 patients (14 %) were classified as having small (≤2 cm) HCC. Histopathologically, MVI was identified in 375 patients (33.8 %), and approximately half of the patients (506; 45.6 %) had cirrhosis. The median follow-up period was 40.3 months (range 1–205).

Long-Term Survival According to Current Staging Systems

Patients' disease was classified on the basis of size of HCC and presence of MVI according to three current staging systems: AJCC 7th edition, LCSGJ 5th edition, and BCLC staging system. Within each staging system, the survival rates of patients with different stages of disease were compared (Fig. 1). The patients were well-stratified by all three staging systems. For patients with stages I and II disease according to the AJCC 7th edition, the median survival durations were estimated to be 84.7 and 60.6 months, respectively ($p < 0.0001$). In the LCSGJ 5th edition and BCLC staging systems, the prognostic advantage associated with small HCC (≤2 cm) was clear: the median survival duration of the LCSGJ stage I was 126.9 months and that of the BCLC stage 0 was 101.3 months, respectively.

Prognostic Impact of MVI in HCC up to 2 cm

In patients with HCC up to 2 cm, long-term survival was not influenced by the presence of MVI ($p = 0.8$). However, in patients with HCC larger than 2 cm, patients with MVI had significantly worse survival ($p < 0.0001$; Fig. 2). The characteristics of patients with tumors up to 2 cm with and without MVI are shown in Table 1. Histologic grade and serum alpha-fetoprotein level were higher in the patients with MVI than in those without MVI. Other demographic and clinical factors did not differ significantly between the two groups.

Prognostic Factors by Tumor Size

In patients with HCC up to 2 cm, none of the studied factors were significantly associated with long-term survival in the univariate analysis (Table 2). However, in patients with HCC larger than 2 cm, three factors were significant predictors of worse overall survival in both univariate and multivariate analysis: presence of MVI (HR 1.59; 95 % CI 1.27–1.99; $p < 0.001$), alpha-fetoprotein level higher than 10 ng/mL (HR 1.41; 95 % CI 1.11–1.8; $p = 0.005$), and higher histologic grade (HR 1.29; 95 % CI 1.01–1.64; $p = 0.04$).[23]

Reclassification of Solitary HCC

On the basis of these results, we reclassified solitary HCC into three groups—up to 2 cm, larger than 2 cm without MVI, and larger than 2 cm with MVI—and compared the survival curves for these groups (Fig. 3a). There were significant prognostic differences among these three groups.

We also compared the survival curves for these three groups with the survival curves generated for the patients with multiple HCC who were identified in our initial search for patients who underwent curative resection of HCC between 1981 and 2011 but excluded from the final cohort because of their multiple HCC. The survival curve of patients with solitary HCC larger than 2 cm with MVI was quite similar to that of patients with multiple HCC up to 5 cm (median survival, 55 versus 55.9 months; $p = 0.53$; Fig. 3b). When we modified the current AJCC 7th edition classification to take into account tumor size and MVI in patients with solitary HCC (Table 3), clear prognostic stratification was obtained, and patients with solitary HCC up to 2 cm had a better prognosis than those with solitary HCC larger than 2 cm (Fig. 3c).

DISCUSSION

In this study, we analyzed the influence of tumor size and MVI on the long-term survival of 1,109 patients with solitary HCC. Our findings indicate that neither MVI nor histologic grade has an impact on long-term survival in patients with HCC measuring up to 2 cm and suggest the possibility of dividing the T1 category in the current AJCC 7th edition staging system into T1a, for patients with solitary HCC up to 2 cm irrespective of MVI, and T1b, for patients with solitary HCC larger than 2 cm without MVI.

To date, various staging systems have been used to stratify patients with HCC with respect to prognosis and to help select optimal therapeutic options for patients with HCC.[17,24–26] In most classification systems, T category is determined by tumor size, tumor number, presence/absence of MVI, presence/absence of major vascular invasion, or tumor invasion or rupture. The current AJCC 7th edition classification is a modification of a simplified staging system established by extensive prognostic analysis of HCC, and its clinical relevance has been validated in various studies.[2–8,26,27] However, a limitation of the current edition of the AJCC classification is that all solitary HCCs without MVI are classified as stage I regardless of tumor size.

In BCLC and other staging systems, HCC measuring up to 2 cm is considered “early HCC” and is associated with a high rate of surgical cure. This specific subset of HCC has been reported to be less oncologically aggressive and is characterized by excellent prognosis after surgical resection, radiofrequency ablation, or transplantation.[9,12–14,28–30] The current study confirms that HCC up to 2 cm is associated with a favorable prognosis: patients with such tumors had a median survival of 10 years after surgical resection. Another noteworthy result is that neither MVI nor histologic grade affected overall survival in patients with HCC measuring up to 2 cm, whereas these pathologic factors were significantly associated with

long-term survival in patients with HCC larger than 2 cm. These data correlate with recent studies from Japan and the west that reported MVI had no significant impact on overall survival in patients with HCC up to 2 cm.[10,31] Although we have not investigated recurrence-free survival, our results are compatible with the results of these studies.

From a clinical standpoint, our results are practically important. First, various curative therapeutic options can be selected for such small tumors, including surgical resection, radiofrequency ablation, or transplantation, according to the underlying liver function and the patient's performance status. Second, because histopathologic features have no effect on the prognosis of patients with HCC up to 2 cm, resection for the purpose of pathologic evaluation might not be necessary in patient selection for liver transplantation.[32,33]

On the basis of these results, we modified the current AJCC classification system by integrating a size cutoff of 2 cm for solitary HCC. When we classified solitary HCC up to 2 cm as T1a, solitary HCC larger than 2 cm without MVI as T1b, and solitary HCC larger than 2 cm with MVI as T2, the current AJCC classification was better able to stratify the outcome of patients with early HCC. Furthermore, the survival curve for solitary HCC larger than 2 cm with MVI was quite similar to that for multiple HCC up to 5 cm. Therefore, these two groups can be grouped together in a revised T2 category.

The limitations of this study include its retrospective nature and selected population. However, the clinical data from each of the six participating hepatobiliary centers were collected prospectively, and importantly, these data are from various countries in North America, Europe, and Asia. In addition, because the current data are for patients treated only with surgical resection, validation using patients who received nonsurgical treatment may be needed. Furthermore, very small number of patients having MVI in small HCC might raise the possibility of type II error in statistical analysis. However, the patients with HCC measuring up 2 cm actually have good prognosis and the current results are consistent with the reported outcomes of two recent studies investigating small HCC.[10,31]

In conclusion, MVI does not affects long-term survival in patients with HCC up to 2 cm. Integration of a size cutoff of 2 cm may improve the ability of the current AJCC staging system to stratify outcomes of patients with small HCC.

Acknowledgments

The authors thank Ms. Stephanie Deming and Ms. Ruth Haynes for their contribution to our manuscript. The University of Texas MD Anderson Cancer Center is supported in part by the National Institutes of Health through Cancer Center Support Grant CA016672.

REFERENCES

1. Edge, SB.; Byrd, DR.; Compton, CC.; Fritz, AG.; Greene, FL.; Trotti, A., editors. AJCC cancer staging manual. 7th ed.. New York: Springer; 2010.
2. Cheng CH, Lee CF, Wu TH, Chan KM, Chou HS, Wu TJ, et al. Evaluation of the new AJCC staging system for resectable hepatocellular carcinoma. World J Surg Oncol. 2011; 9:114. [PubMed: 21958080]
3. Kee KM, Wang JH, Lee CM, Chen CL, Changchien CS, Hu TH, et al. Validation of clinical AJCC/UICC TNM staging system for hepatocellular carcinoma: analysis of 5,613 cases from a medical center in southern Taiwan. Int J Cancer. 2007; 120:2650–2655. [PubMed: 17304512]
4. Lei HJ, Chau GY, Lui WY, Tsay SH, King KL, Loong CC, et al. Prognostic value and clinical relevance of the 6th Edition 2002 American Joint Committee on Cancer staging system in patients with resectable hepatocellular carcinoma. J Am Coll Surg. 2006; 203:426–435. [PubMed: 17000385]

5. Poon RT, Fan ST. Evaluation of the new AJCC/UICC staging system for hepatocellular carcinoma after hepatic resection in Chinese patients. Surg Oncol Clin N Am. 2003; 12:35–50. viii. [PubMed: 12735128]
6. Ramacciato G, Mercantini P, Cautero N, Corigliano N, Di Benedetto F, Quintini C, et al. Prognostic evaluation of the new American Joint Committee on Cancer/International Union Against Cancer staging system for hepatocellular carcinoma: analysis of 112 cirrhotic patients resected for hepatocellular carcinoma. Ann Surg Oncol. 2005; 12:289–297. [PubMed: 15827681]
7. Varotti G, Ramacciato G, Ercolani G, Grazi GL, Vetrone G, Cescon M, et al. Comparison between the fifth and sixth editions of the AJCC/UICC TNM staging systems for hepatocellular carcinoma: multicentric study on 393 cirrhotic resected patients. Eur J SurgOncol. 2005; 31:760–767.
8. Wu CC, Cheng SB, Ho WM, Chen JT, Liu TJ, P'Eng FK. Liver resection for hepatocellular carcinoma in patients with cirrhosis. Br J Surg. 2005; 92:348–355. [PubMed: 15672423]
9. Takayama T, Makuuchi M, Hirohashi S, Sakamoto M, Yamamoto J, Shimada K, et al. Early hepatocellular carcinoma as an entity with a high rate of surgical cure. Hepatology. 1998; 28:1241–1246. [PubMed: 9794907]
10. Yamashita YI, Tsuijita E, Takeishi K, Fujiwara M, Kira S, Mori M, et al. Predictors for microinvasion of small hepatocellular carcinoma ≤ 2 cm. Ann Surg Oncol. 2012; 19:2027–2034. [PubMed: 22203184]
11. Inoue K, Takayama T, Higaki T, Watanabe Y, Makuuchi M. Clinical significance of early hepatocellular carcinoma. Liver Transplant. 2004; 10:S16–S19.
12. Todo S, Furukawa H. Living donor liver transplantation for adult patients with hepatocellular carcinoma: experience in Japan. Ann Surg. 2004; 240:451–459. discussion 59–61. [PubMed: 15319716]
13. Livraghi T, Meloni F, Di Stasi M, Rolle E, Solbiati L, Tinelli C, et al. Sustained complete response and complications rates after radiofrequency ablation of very early hepatocellular carcinoma in cirrhosis: is resection still the treatment of choice? Hepatology. 2008; 47:82–89. [PubMed: 18008357]
14. Arii S, Yamaoka Y, Futagawa S, Inoue K, Kobayashi K, Kojiro M, et al. Results of surgical and nonsurgical treatment for small-sized hepatocellular carcinomas: a retrospective and nationwide survey in Japan. The Liver Cancer Study Group of Japan. Hepatology. 2000; 32:1224–1229. [PubMed: 11093728]
15. Liver Cancer Study Group of Japan. The general rules for the clinical and pathological study of primary liver cancer. 5th ed.. Tokyo: Kanehara; 2008.
16. Llovet JM, Burroughs A, Bruix J. Hepatocellular carcinoma. Lancet. 2003; 362:1907–1917. [PubMed: 14667750]
17. Liver Cancer Study Group of Japan. Primary liver cancer in Japan. Clinicopathologic features and results of surgical treatment. Liver Cancer Study Group of Japan. Ann Surg. 1990; 211:277–287. [PubMed: 2155591]
18. Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med. 1996; 334:693–699. [PubMed: 8594428]
19. Makuuchi M, Belghiti J, Belli G, Fan ST, Lau JW, Ringe B, et al. IHPBA concordant classification of primary liver cancer: working group report. J Hepatobiliary Pancreatic Surg. 2003; 10:26–30.
20. Jonas S, Bechstein WO, Steinmuller T, Herrmann M, Radke C, Berg T, et al. Vascular invasion and histopathologic grading determine outcome after liver transplantation for hepatocellular carcinoma in cirrhosis. Hepatology. 2001; 33:1080–1086. [PubMed: 11343235]
21. Edmondson HA, Steiner PE. Primary carcinoma of the liver: a study of 100 cases among 48,900 necropsies. Cancer. 1954; 7:462–503. [PubMed: 13160935]
22. Ishak K, Baptista A, Bianchi L, Callea F, De Groote J, Gudat F, et al. Histological grading and staging of chronic hepatitis. J Hepatol. 1995; 22:696–699. [PubMed: 7560864]
23. Rahbari NN, Mehrabi A, Mollberg NM, Muller SA, Koch M, Buchler MW, et al. Hepatocellular carcinoma: current management and perspectives for the future. Ann Surg. 2011; 253:453–469. [PubMed: 21263310]

24. The Cancer of the Liver Italian Program (CLIP) Investigators. A new prognostic system for hepatocellular carcinoma: a retrospective study of 435 patients: The Cancer of the Liver Italian Program (CLIP) Investigators. Hepatology. 1998; 28:751–755. [PubMed: 9731568]
25. Llovet JM, Bru C, Bruix J. Prognosis of hepatocellular carcinoma: the BCLC staging classification. Semin Liver Dis. 1999; 19:329–338. [PubMed: 10518312]
26. Vauthey JN, Lauwers GY, Esnaola NF, Do KA, Belghiti J, Mirza N, et al. Simplified staging for hepatocellular carcinoma. J Clin Oncol. 2002; 20:1527–1536. [PubMed: 11896101]
27. Vauthey JN, Ribero D, Abdalla EK, Jonas S, Bharat A, Schumacher G, et al. Outcomes of liver transplantation in 490 patients with hepatocellular carcinoma: validation of a uniform staging after surgical treatment. J Am Coll Surg. 2007; 204(5):1016–1027. [PubMed: 17481532]
28. Kanai T, Hirohashi S, Upton MP, Noguchi M, Kishi K, Makuuchi M, et al. Pathology of small hepatocellular carcinoma. A proposal for a new gross classification. Cancer. 1987; 60:810–819. [PubMed: 2439190]
29. Tsuda H, Zhang WD, Shimosato Y, Yokota J, Terada M, Sugimura T, et al. Allele loss on chromosome 16 associated with progression of human hepatocellular carcinoma. Proc Natl Acad Sci USA. 1990; 87:6791–6794. [PubMed: 2168560]
30. Kojiro M, Yano H, Nakashima O. Pathology of early hepatocellular carcinoma: progression from early to advanced. Semin Surg Oncol. 1996; 12:197–203. [PubMed: 8727611]
31. Roayaie S, Obeidat K, Sposito C, Mariani L, Bhoori S, Pellegrinelli A, et al. Resection of hepatocellular cancer ≤ 2 cm: results from two western centers. Hepatology. 2012 (accepted).
32. Sala M, Fuster J, Llovet JM, Navasa M, Sole M, Varela M, et al. High pathological risk of recurrence after surgical resection for hepatocellular carcinoma: an indication for salvage liver transplantation. Liver Transplant. 2004; 10:1294–1300.
33. Belghiti J, Cortes A, Abdalla EK, Regimbeau JM, Prakash K, Durand F, et al. Resection prior to liver transplantation for hepatocellular carcinoma. Ann Surg. 2003; 238:885–892. discussion 92–3. [PubMed: 14631225]

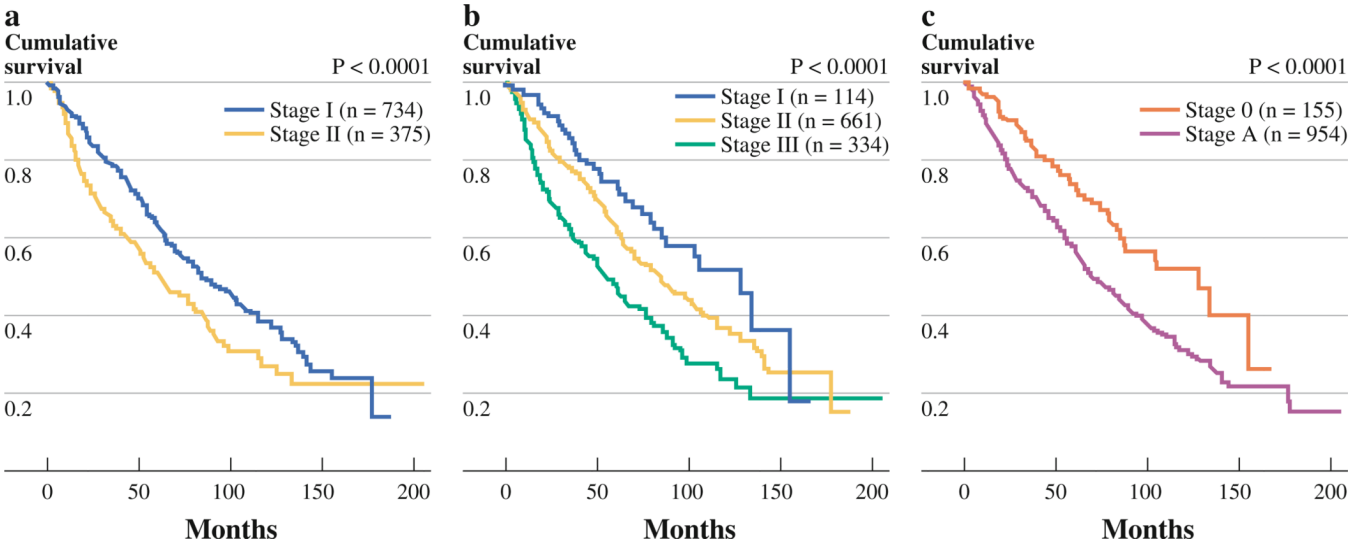

FIG. 1.

Survival of patients with solitary hepatocellular carcinoma according to current staging systems. **a** American Joint Committee on Cancer 7th edition. **b** Liver Cancer Study Group of Japan 5th edition. **c** Barcelona Clinic Liver Cancer staging system

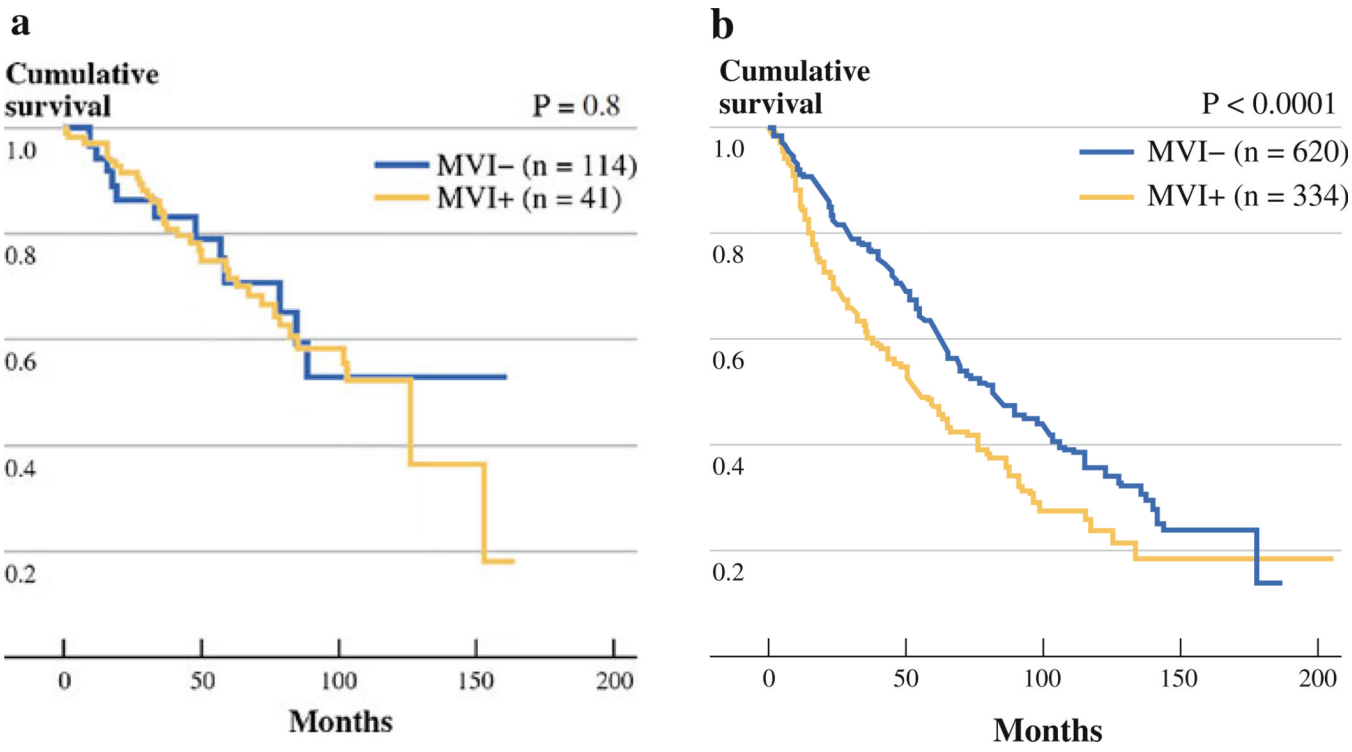

FIG. 2.

Survival of patients with solitary hepatocellular carcinoma according to presence of microvascular invasion (MVI). **a** Tumor size 0–2 cm.
b Tumor size >2 cm

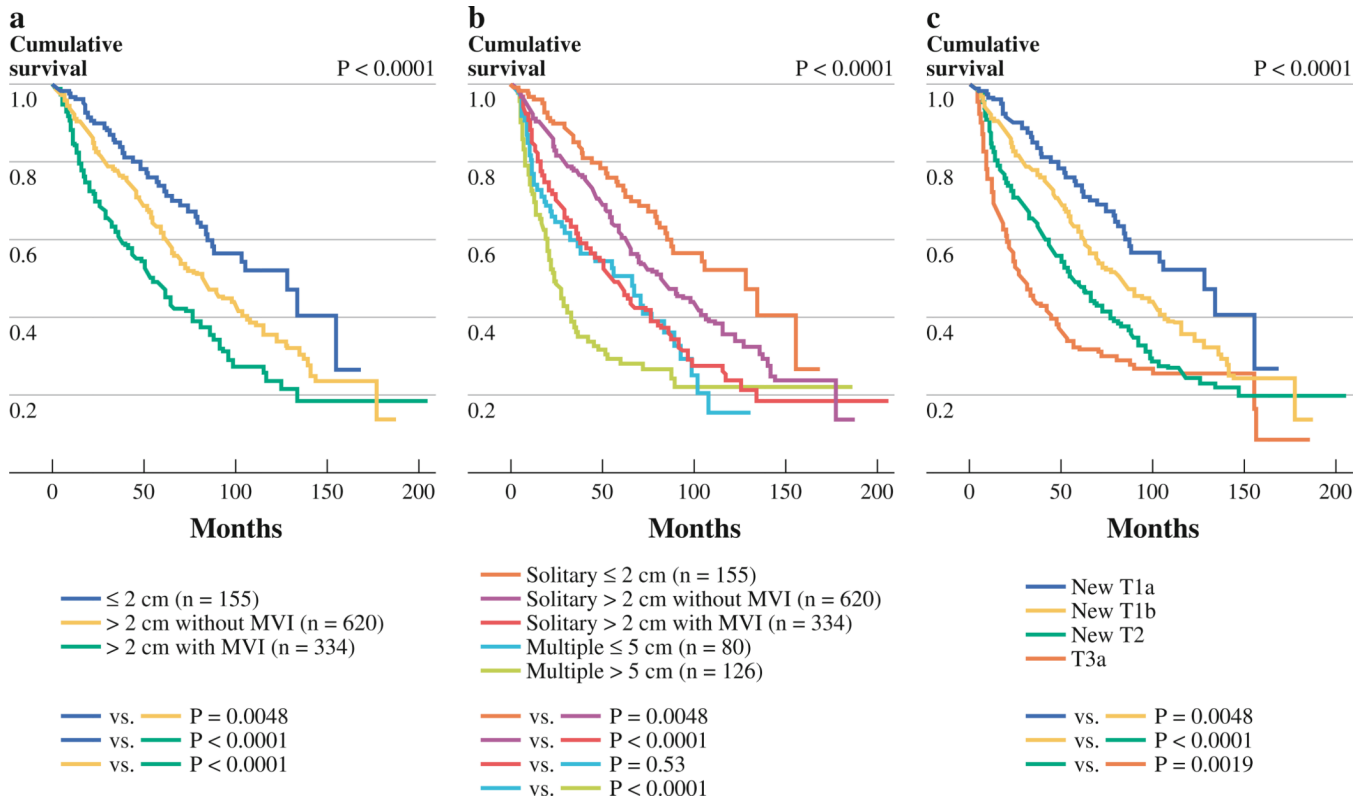

FIG. 3.

Survival of patients with solitary hepatocellular carcinoma according to tumor size and microvascular invasion (MVI) and new classification of hepatocellular carcinoma (HCC). **a** Comparison of survival according to size cutoff value of 2 cm and MVI. **b** Comparison of new classification for solitary tumor and current classification of multiple HCC. **c** Proposed new classification by stage (stages as outlined in Table 3)

TABLE 1

Characteristics of patients with HCC up to 2 cm by MVI status

Characteristic	MVI− (*n* = 114)	MVI+ (*n* = 41)	*p*
Age (years), median (range)	62.5 (28–82)	63 (11–78)	0.57
Gender, male	86 (75.4)	27 (65.9)	0.24
Hepatitis C positive[a]	42 (36.8)	17 (41.5)	0.59
Hepatitis B positive[b]	40 (35.1)	17 (41.5)	0.77
Child–Pugh class			0.54
A	102 (89.5)	38 (92.7)	
B	12 (10.5)	3 (7.3)	
Tumor size (cm), median (range)	1.7 (0.5–2.0)	1.8 (0.9–2.0)	0.42
Histologic grade[c]			0.04
Well differentiated	26 (24.3)	2 (4.9)	
Moderately differentiated	64 (59.8)	28 (68.3)	
Poorly differentiated	17 (15.9)	11 (26.8)	
Unknown	7 (6.1)	0 (0)	
Liver cirrhosis[d]	69 (60.5)	24 (58.5)	0.82
AFP (ng/mL), median (range)	14 (1–6417)	82 (1.6–135094)	0.02
Type of resection			0.82
Minor	105 (92.1)	38 (92.7)	
Major	9 (7.9)	3 (7.3)	
Microscopic margin status			0.31
Positive	2 (1.9)	2 (4.9)	
Negative	105 (98.1)	39 (95.1)	

Values are number of patients (percentage) unless otherwise indicated *HCC* hepatocellular carcinoma, *MVI* microvascular invasion, *AFP* alpha-fetoprotein

[a] Missing data in 33 cases

[b] Missing data in 11 cases

[c] Edmondson grade[21]

[d] Ishak score F5 or F6[22]

TABLE 2

Prognostic factors in HCC >2 cm

	HCC ≤ 2 cm (*n* = 155)					HCC > 2 cm (*n* = 954)							
	N	5-Year survival	Univariate analysis			*N*	5-Year survival	Univariate analysis			Multivariate analysis		
			HR	95 % CI	*p*			HR	95 % CI	*p*	HR	95 % CI	*p*
Age (years)													
>65	65	77.3	0.76	0.4–1.36	0.36	363	55.6	1.07	0.88–1.3	0.49			
0–65	90	72.3				591	57.1						
Sex													
Male	113	74.5	1.2	0.64–2.42	0.59	696	55.9	1.04	0.84–1.29	0.75			
Female	42	73.4				258	58.3						
HCV													
Positive	59	83.9	0.63	0.3–1.31	0.21	265	66.4	0.81	0.63–1.11	0.11			
Negative	63	67.1				360	54.7						
HBV													
Positive	57	75.6	0.89	0.46–1.70	0.74	344	48.6	1.3	1.05–1.59	0.01	1.21	0.97–1.51	0.08
Negative	67	73.9				508	60.7						
Child–Pugh													
B	15	81.3	0.71	0.21–1.77	0.5	64	60.1	0.77	0.51–1.11	0.17			
A	140	72				890	56.6						
Microvascular invasion													
Present	41	71.3	0.92	0.46–1.72	0.8	620	47.3	1.55	1.27–1.87	<0.0001	1.59	1.27–1.99	<0.001
Absent	114	75				334	61.4						
Background liver													
Cirrhosis	93	73.1	1.52	0.83–3	0.18	413	55.2	1.06	0.88–1.28	0.55			
Noncirrhosis	62	75.4				529	57.2						
AFP (ng/mL)													
>10	94	72.1	1.09	0.61–2.01	0.78	566	53.9	1.27	1.04–1.56	0.02	1.41	1.11–1.8	0.005
0–10	61	77.4				355	62						
Histologic grade[a]													

	HCC ≤ 2 cm (*n* = 155)					HCC > 2 cm (*n* = 954)							
	N	**5-Year survival**	**Univariate analysis**			***N***	**5-Year survival**	**Univariate analysis**			**Multivariate analysis**		
			HR	**95 % CI**	***p***			**HR**	**95 % CI**	***p***	**HR**	**95 % CI**	***p***
G3–4	28	76.2	1.27	0.6–2.47	0.51	263	47.7	1.5	1.22–1.84	0.0001	1.29	1.01–1.64	0.04
G1–2	120	72.6				664	59.7						
Surgery													
Minor	143	73.2	0.8	0.29–3.32	0.72	586	58.9	0.89	0.73–1.08	0.22			
Major	12	90.9				368	52.8						

HCC hepatocellular carcinoma, *HCV* hepatitis C virus, *HBV* hepatitic B virus, *AFP* alpha-fetoprotein, *HR* hazard ratio, *CI* confidence interval

[a]Edmondson grade: G1, well differentiated; G2, moderately differentiated; G3, poorly differentiated; G4, undifferentiated

TABLE 3

Current AJCC classification (7th edition) and new classification

AJCC 7th edition		OS (months), median (range)	New classification		OS (months), median (range)
T1	Solitary HCC without MVI	84.7 (76.1–100.4)	**T1a**	**Solitary HCC ≤2 cm**	126.9 (83.8–NE)
			T1b	**Solitary HCC >2 cm without MVI**	81.4 (69–97.2)
T2	Solitary HCC with MVI	60.6 (50.4–75.8)	**T2**	**Solitary HCC >2 cm with MVI**	55.0 (44.2–65.6)
	Multiple HCC ≤5 cm	55.9 (48.6–72)		Multiple HCC ≤5 cm	55.9 (48.6–72)
T3a	Multiple HCC >5 cm	27.7 (22.5–38.7)	T3a	Multiple HCC >5 cm	27.2 (22.5–38.7)
T3b	Major vascular invasion	28 (15.4–43.3)	T3b	Major vascular invasion	28 (15.4–43.3)

AJCC American Joint Committee on Cancer, *OS* overall survival, *NE* not estimated, *HCC* hepatocellular carcinoma, *MVI* microvascular invasion

T-stages redefined according to the new proposed classification are in bold

Ann Surg Oncol. Author manuscript; available in PMC 2014 April 01.